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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,989	05/29/2001	Wilfred Wayne Lautt	2495.00071	7861

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ART UNIT	**PAPER NUMBER**
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/806,989	LAUTT, WILFRED WAYNE	
	Examiner	Art Unit	
	Charleswort Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 19-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/26/07;2/21/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, filed 2/21/07, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Applicant's statements that support of the term "therapeutic" to claim 1 can be found throughout the specification, including page 11, line 20 to page 12, line 2, while support for the specific nitric oxide donor compounds recited in claim 29 can be found at page 8, lines 11-15 and throughout the specification, are acknowledged and made of record. Applicant's statement that no new matter has been added by the amendment is also acknowledged and made of record.

Applicant's Interview Summary memoralizing the interview of November 16, 2006, is also acknowledged and made of record.

Status of the Claims

Claims 1-3 and 19-20 are currently pending in this application and are the subject of this Office action.

Claim 20 has been added.

Response to arguments

Applicant asserts that the rejection of claims 1-3 and 19 under 112, second paragraph, should be withdrawn in view of the amendment of claim 1, reciting the term

"the patient" in place of the term "a patient." This rejection is withdrawn in view of the amendment.

Applicant asserts that the rejection under 102(b) should be withdrawn in view of the amendment of the claims. This rejection is withdrawn in view of the amendment.

New Rejections

Claims 1-3 and 19-20 are rejected under 112, first paragraph, for lack of scope of enablement for reasons stated below.

Claims 1-3 and 19-20 are rejected under 103(a) as being unpatentable over Adams et al. and Lautt et al. for the reasons stated below.

Restriction/Election

Applicant's election with traverse of Group I (claims 1-2 and 8-17) and the ABX-EGF species in the reply on May 23, 2006, is acknowledged. The traversal is on the ground that it would not be unduly burdensome to search the claims. This is not found persuasive because applicant has only asserted a conclusory statement without pointing out any supposed errors in the restriction to support the conclusion.

The requirement is still deemed proper and is therefore made FINAL.

With respect to the election of the species ABX-EGF, this election requirement is being withdrawn for examination purposes. All species of EGFR inhibitor are under examination.

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain therapeutic nitric oxide donor compounds, including 3-morpholinisyndnonimine (SIN-1), sodium nitrite, nitroprusside, and S-nitroso-N-acetyl-D, L-penicillamine (SNAP), (see Specification, page 8, lines 11-15), does not reasonably provide enablement for any therapeutic nitric oxide donor compound. This is a scope enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The invention in general relates to a method of increasing insulin sensitivity in a mammalian patient comprising administering an effective amount of a nitric oxide donor compound.

Applicant discloses that following a meal, the parasympathetic reflex mechanism is amplified so that HISS release occurs and results in the majority of te ingested glucose being stored in skeletal muscle (page 4, lines 19-21). Applicant discloses that there has been no evidence of compounds which can be used to control or alter the pathway involving HISS (page 5, line 4 to page 6, line 2). Applicant asserts that instant

invention provides a method of increasing insulin sensitivity by administering an effective amount of a compound which stimulates nitric oxide production in the liver and a pharmaceutical composition having an effective amount of a compound which stimulates nitric oxide production in the liver (page 6, lines 10-15). Applicant discloses that nitric oxide can be administered to the liver by provision of nitric oxide donors or nitric oxide agonists or compounds that generate nitric oxide within the liver when administered orally, intravenously, intramuscularly, subcutaneously, or by delivery through a pump system directly into the portal vein; ideally such a compound would be administered prior to a meal in order to restore normal hepatic parasympathetic responses to insulin and thereby restore insulin sensitivity (page 10, lines 13-17). Applicant discloses that "the pharmaceutically effective amount" is determined by such considerations as are known in the art (page 11, lines 27 to page 12, line 2). Applicant discloses that insulin resistance is produced by the blockade of nitric oxide synthase which is not reversed by administration of a nitric oxide donor intravenously but is fully reversed by administration of the same dose directly to the liver via portal vein (page 30, lines 11-15 i.e. Example 3). Applicant discloses that depending on the pathology, insulin resistance can be restored to normal by administration of a cholinergic agonist or a source of nitric oxide (page 30, lines 20-26).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the pharmaceutical art is generally unpredictable, requiring each embodiment to be individually assessed for physiological activity. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re*

Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)). For example, applicant discloses that insulin resistance is produced by the blockade of nitric oxide synthase which is not reversed by administration of a nitric oxide donor intravenously, but is fully reversed by administration of the same dose directly to the liver via portal vein (page 30, lines 11-15 i.e. Example 3). Applicant also discloses that depending on the pathology, insulin resistance can be restored to normal by administration of a cholinergic agonist or a source of nitric oxide (page 30, lines 20-26). Thus, the mechanism by which insulin sensitivity can be increased is dependent on multiple factors.

Lautt et al. (US Patent 5,561,165) teach a method for increasing insulin responsiveness and improving glucose tolerance in a mammal in which insulin responsiveness and glucose tolerance are impaired comprising administering an effective amount of a cholinergic agent (column 1, lines 35-40). Lautt et al. teach that non-insulin dependent diabetes mellitus (NIDDM) may show insulin resistance and impaired glucose tolerance, as well as parasympathetic neuropathies; patients with chronic liver disease also show insulin resistance (column 1, lines 9-14).

Adam (US Patent 6,165,975; already made of record) teach a method of treatment, in an organism, of a vascular condition, comprising administration of at least one agent at a level which enhances NO and which does not appreciably alter normal systemic vascular tone in said organism. At least one agent is an NO donor selected from the group consisting of glyceryl trinitrate, isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside, 3-morpholinosydnonimine molsidomine, S-nitroso-N-acetylpenicillamine, S-

nitrosoglutathione, and N-hydroxy-L-arginine (see abstract). Adams et al. also teach that No compounds, or compounds which deliver NO, can provoke powerful vasodilator responses, which is often accompanied by a number of undersirable side effects (column 1, lines 24-29).

Literati Nagy et al. (US Patent 6,887,872 B2) teach that only in fed state, nitrogen oxide causes the release of a hepatic insulin sensitizing factor (HISS) which possesses insulin synergent or insulin-like effect (column 19, lines 56-58).

The unpredictability or uncertainty in the art is illustrated by the fact that applicant that applicant asserts that ideally NO donor compounds should be administered prior to a meal in order to restore normal hepatic parasympathetic responses to insulin and thereby restore insulin sensitivity (page 10, lines 13-17), while Literarti Nagy et al. teach that only in the fed state, nitrogen oxide causes the release of a hepatic insulin sensitizing factor (HISS) which possesses insulin synergent or insulin-like effect (column 19, lines 56-58).

Thus, one skilled in the art would not be able to extrapolate the disclosed teachings of the claimed invention to increase insulin sensitivity in all mammalian patients in need thereof for NO donors.

2. The breadth of the claims

The claims are all relatively broad as they encompass all mammalian species, and multiple routes of administering NO donors. Applicant has disclosed as stated above that different routes of administration leads to different treatment outcomes. Claims 1-3 and 19 reasonably encompass all therapeutic nitric oxide donor

compounds, including compounds that may be discovered in the future. Although therapeutic nitric oxide donors may impliedly all release nitric oxide, the actual site of release of the NO compound, and the acutal amount of nitric oxide released following the administration of a particular therapeutic NO donor, would reasonably vary widely depending on the factors discussed above relating to route of administration, underlying pathology of the targeted condition to be treated, and the inherent pharmaceutical properties of the specific therapeutic NO donor. Thus, the level of predictably in practicing the claimed invention would be greatly diminished.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance to reasonably predict the amount of nitric oxide that would be released preferentially, or otherwise, in the liver to achieve the contemplated effect of increasing insulin sensitivity in a mammalian patient following the administering of any therapeutic NO donor.

The 'working examples" are limited to a single example involving SIN-1 (specification, page 9, line 17 to page 10, line 5; page 10, lines 13-17, and page 23, lines 1-5).

4. The quantity of experimentation necessary

In view of applicant's disclosure and the teaching in the prior art of potential serious side effects associated with the administration of NO donors, it is reasonable to surmise that the level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention, in the absence of pharmaceutical and pharmacokinetic data regarding the

encompassed therapeutic NO donors. Thus, someone of skill in the art would not be able to reasonably and predictably practice the instant claimed invention commensurate with its full scope without performing under experimentation.

For the reasons stated above, claims 1-3 and 19-20 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, and 19-20 are rejected as being unpatentable over Adams et al. (US Patent 6,165,975; already made of record), in view of Lautt et al. (US Patent 5,561,165).

Adam et al. teach a method of treatment, in an organism, of a vascular condition, comprising administration of at least one agent at a level which enhances NO and which does not appreciably alter normal systemic vascular tone in said organism. At least one agent is an NO donor selected from the group consisting of glyceryl trinitrate, isosorbide 5-mononitrate, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, sodium nitroprusside, 3-morpholinosydnonimine molsidomine, S-nitroso-N-acetylpenicillamine, S-nitrosoglutathione, and N-hydroxy-L-arginine (see abstract); instant claim 20 specifically recites these NO donor compounds. Adams et al. also teach that NO, in humans and animals, produced via sodium nitroprusside (SNP) infusion, causes vasodilation in peripheral vasculature at doses greater than 10 micrograms/kg per minute (column 1, line 66 to column 2, line 4); SNP may be administered in a convenient manner such as by injection (column 15, lines 35-37). Instant claim 1 recites the limitation "orally administering the compound", which is reasonably met by the reference (column 16, lines 41-53). Instant claim 3 recites the limitation "injecting the compound," which is reasonably met by the reference (column 15, lines 35-37). Adams et al. also teach that No performs a function through interaction with endothelin (ET), and that ET is under inhibitory control of NO, such that administration of NOS inhibitors results in elevated levels of ET (column 2, lines 2-11). Adams et al. also disclose that a number of investigators have postulated that ET antagonists could be used for conditions including diabetes (column 2, lines 24-31).

Although Adams et al. do not specifically teach the limitation of hepatic sensitizing substance (HISS) dependent insulin sensitivity as recited in claim 19, this activity is construed to be coextensive with the administration of a therapeutic nitric oxide donor compound. To the extent that Adams et al. teach a method of treatment comprising administering NO donors, these compounds are reasonably construed to be "therapeutic nitric oxide donor compound."

Lautt et al. (US Patent 5,561,165) teach a method for increasing insulin responsiveness and improving glucose tolerance in a mammal in which insulin responsiveness and glucose tolerance are impaired comprising administering an effective amount of a cholinergic agent (column 1, lines 35-40). Lautt et al. teach that non-insulin dependent diabetes mellitus (NIDDM) may show insulin resistance and impaired glucose tolerance, as well as parasympathetic neuropathies, and that patients with chronic liver disease also show insulin resistance (column 1, lines 9-14).

Based on the teaching of Lautt et al., someone of skill at the time the instant claimed invention was made would have been motivated to combine the teaching of Adams et al. and Lautt et al. to create a method for increasing insulin sensitivity in a diabetic patient comprising administering the NO donor compounds taught by Adams et al. Thus, someone of skill in the art at the time the instant invention was made would have deemed it obvious to create the instant claimed invention with a reasonable expectation of success in view of Adams et al. and Lautt et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-

6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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12 May 2007
CER

BRIAN-YONG S. KWON
PRIMARY EXAMINER